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Ana Rita Moreira Coelho

Diabetes Mellitus in HIV-infected patients: fasting glucose, A1C or oral glucose tolerance test - which method to choose for the diagnosis?

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Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Endocrinologia

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Diabetes Mellitus in HIV-infected patients: fasting glucose, A1C or oral glucose tolerance test - which method to choose for the diagnosis?

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Para os meus pais e para o Francisco.

Obrigado pelo amor e apoio incondicionais.

DIABETES MELLITUS IN HIV-INFECTED PATIENTS: FASTING GLUCOSE, A1C OR ORAL GLUCOSE TOLERANCE TEST – WHICH METHOD TO CHOOSE FOR THE DIAGNOSIS?

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ABSTRACT

Background: Antiretroviral therapy dramatically reduced HIV-related morbidity and mortality and prolonged the lifespan of HIV-infected patients. A greater duration of infection and exposure to antiretroviral therapy makes these patients susceptible to traditional cardio-metabolic risk factors and pathologies. The optimal diagnostic protocol for Diabetes Mellitus in these patients is still controversial. HbA1c has been shown to underestimate glycaemia levels and oral glucose tolerance test (OGTT) as been shown to reveal cases of glucose metabolism disturbances in patients with normal fasting glucose (FG). Thus, this study aimed to determine the prevalence of Prediabetes and Diabetes, in a population of HIV-infected patients under combined antiretroviral therapy, using three different diagnostic methods (FG, OGTT and HbA1c), to determine the agreement between the different methods and the characteristics associated with each one.

Methods: This study analyzed 220 HIV-infected patients on antiretroviral therapy. Patient characteristics were collected using a standardized protocol. Disturbances of glucose homeostasis were defined by the American Diabetes Association 2017 criteria. Patients were characterized according to the presence or absence of clinical lipodystrophy, and also distributed into four different categories according the presence or absence of either clinical lipoatrophy or abdominal prominence. Insulin resistance was assessed by HOMA-IR and QUICKI indexes. Agreement between the diagnostic methods was assessed by Cohen's kappa coefficient.

Results: There were no patients diagnosed with Diabetes with HbA1c. 5,9% prevalence was obtained when OGTT was used and 3,2% prevalence when FG

was used. Prediabetes had a prevalence of 14,1% when using HbA1c, 24,1% when using OGTT and 20% when using FG. In all three methods, glucose homeostasis disturbances were associated with older age and higher resistance to insulin. Regarding other characteristics, associations varied between the three methods. The agreement between them was fair or slight.

Conclusions: We observed that HbA1c was the method that diagnosed the least amount of cases and that OGTT was the one that diagnosed the most cases. Thus, our results indicate that HbA1c underestimated glycaemia levels in this population and that the use of OGTT might allow an earlier diagnosis of glucose homeostasis disturbances, potentially making it possible to avoid severe complications of DM.

Keywords: HIV infection, Diabetes Mellitus diagnosis, Fasting glucose, Oral Glucose Tolerance Test, HbA1c

BACKGROUND

Despite the worldwide steady increase in the number of people living with HIV/AIDS throughout the years, reaching 38.8 million in 2015, the associated mortality has declined, from a peak of 1.8 million deaths in 2005 to 1.2 million in 2015 [1]. Antiretroviral therapy (ART) dramatically reduced HIV-related morbidity and mortality and prolonged the lifespan of this population [2]. A greater duration of diagnosed HIV infection makes these patients susceptible to exposure to the same traditional cardio-metabolic risk factors and pathologies as

the general population. These complications likely correlate with age, but also with cumulative exposure to ART [2-6].

Cardio-metabolic pathology is, in fact, becoming an increasing problem associated with HIV infection under ART [3, 6, 7]. In a large-scale HIV population study, De Wit et al. have found that the incidence of new-onset diabetes mellitus (DM) increased with cumulative exposure to ART [6]. In fact, it has been shown that HIV populations can have up to two-fold higher risk of DM compared to the general population [5]. Besides ART, traditional risk factors, such as family history, obesity, older age, race, abdominal proeminence and statin use, have also been associated with the development of DM in this population [5, 8, 9].

DM has been identified, in the general population, as a high- and very high-risk factor for the development of cardiovascular disease [10]. This was also demonstrated for the HIV population, in which it was revealed that DM is a risk factor that substantially increases the chance to develop coronary heart disease, especially in prolonged infection [7]. Thus, it is essential to regularly screen for this condition in this population in order to prevent these kinds of complications.

The optimal diagnostic methodology for DM in HIV patients is still a controversial topic. The current EACS guidelines recommend as an initial assessment of glucose metabolism, in patients with new HIV diagnostic and also prior to starting ART, the evaluation of fasting glucose (FG). An oral glucose tolerance test (OGTT) or haemoglobin A1c (HbA1c) measurement is recommended only if FG levels reveal prediabetes (preDM) [11].

The ability to use HbA1c to screen HIV-infected patients in a nonfasting state and estimate long-term glycaemia makes it a very useful tool in the management of DM [12]. However, several authors have now shown that HbA1c underestimates

glycaemia levels in these patients, making it a less accurate diagnostic method [5, 13-16]. In fact, Eckhardt et al. have shown HbA1c to be very insensitive but highly specific in the diagnosis of DM in HIV patients [12]. In light of this evidence, the 2017 American Diabetes Association (ADA) guidelines state that this test underestimates glycaemia in HIV-infected individuals, and that it is not recommended for diagnosis and even for monitoring it may present challenges [17].

On the other hand, the OGTT has been shown to reveal cases of preDM, and even DM, in individuals with normal FG levels [18, 19]. Thus, the use of this test might be an effective method to detect these disturbances of glucose metabolism prematurely, making it possible to avoid the severe complications of the disease by means of an early diagnosis [18].

Due to the fact that the HIV population has the potential to develop cardio-metabolic abnormalities through multiple pathways, determining the magnitude of DM in this population highlights the need for preventive and management strategies. Overall, the optimal diagnostic algorithm is still poorly defined, and the question remains if clinicians should use direct measures of glycaemia or HbA1c to achieve a more accurate diagnosis.

Therefore, this study aims to determine the prevalence of preDM and DM using three differences diagnostic methods (FG, OGTT and HbA1c) in a population of HIV-infected patients under combined antiretroviral therapy (cART). Additionally, it is our aim to investigate which characteristics differ in each diagnostic method between the different groups, and which is the agreement that exists between the different methods.

METHODS

Subjects

As part of a cross-sectional study, between 2005 and 2016, 220 non-institutionalized HIV-infected adults, consecutively referred from the Infectious Diseases Department, were evaluated at the Endocrinology Outpatient Clinic of São João Hospital. Patients were included in the study on the first visit and only patients on cART were included. History of DM and use of anti-diabetic therapy excluded the patients from our study. The Ethics Committee for Health of Hospital São João approved this study and each patient provided written informed consent.

Clinical assessment

For each patient the following information was collected using a standardized protocol: age, known duration of HIV infection and of ART exposure, type of ART currently used, HIV infection risk factors and characterization of the infection, smoking history (past, current, or never), history of diabetes and hypertension, and use of anti-diabetic, anti-hypertensive, and lipid lowering drugs. We used the Centers for Disease Control and Prevention criteria for classifying the degree the infection [20].

Weight, height and abdominal circumference were measured, and Body Mass Index (BMI) was calculated. Body weight was measured using TANITA (Tanita®, model TBF 300) scale and height was measured to the nearest centimeter in the standing position using a wall stadiometer (Holtain Limited Crymych, Dyfed®). BMI was calculated as weight divided by height squared (kg/m2). The waist

circumference (WC) was measured midway between the lowest rib and iliac crest, at the end of a gentle expiration, with the patient standing upright, face directed forward and shoulders relaxed.

Clinical lipodystrophy was defined as peripheral lipoatrophy with or without central fat accumulation assessed by both patient and practitioner [21]. Patients with at least one light, moderate or severe subjective lipoatrophic feature, identified by lipoatrophy-specific physical examination, were asked to report whether he/she had had any change in fat in the cheeks next to the nose, lateral aspect of the face, legs, arms or buttocks. Patients were classified as without peripheral lipoatrophy, when none of the previously described features were present [22]. Presence of central fat accumulation or abdominal prominence was defined by the measurement of WC using the International Diabetes Federation (IDF) criteria for metabolic syndrome (WC ≥ 94cm for Europid men and ≥ 80cm for Europid women). Patients were classified into four different categories according the presence or absence of either clinical lipoatrophy or abdominal prominence: 1) no lipodystrophy – patients without lipoatrophy and without abdominal prominence; 2) isolated central fat accumulation – patients without lipoatrophy and with abdominal prominence; 3) lipoatrophy – patients with lipoatrophy and without abdominal prominence; 4) mixed forms of lipodystrophy – patients with lipoatrophy and with abdominal prominence [22]. The clinical assessment was performed by the same practitioner (PF).

Laboratory analysis

A venous blood sample was taken after a 12-hour overnight fast. All the samples were analyzed at the central laboratory of our hospital. The measurements of

total cholesterol (TC), low density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, plasma glucose and HbA1c serum levels were determined using commercial kits. Hepatitis C was diagnosed by HCV-Ab serostatus.

All patients without a previous diagnosis of diabetes were submitted to an OGTT. The OGTT was performed as described by the World Health Organization using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

The CD4 cell count was determined by flow cytometry and plasma HIV-1 RNA loads were measured by a quantitative reverse transcriptase polymerase chain reaction (Roche Diagnostic Systems, Inc., Branchburg, NJ, USA), which has a lower limit of detection of 50 copies/mL.

Criteria for the definition of disturbances of glucose homeostasis

Disturbances of glucose homeostasis were defined by the ADA 2017 criteria [23]. Patients were divided into three groups: no diabetes (No DM), prediabetes (preDM) and diabetes (DM). No DM was defined as FG <100 mg/dL, HbA1c <5.7% or 120 minutes plasma glucose <140 mg/dL during the OGTT. PreDM was defined as FG between 100 and 126 mg/dL, HbA1c between 5.7% and 6,5% or 120 minutes plasma glucose between 140 and 200 mg/dL during the OGTT. DM was defined as FG ≥126 mg/dL, HbA1c ≥6,5% or 120 minutes plasma glucose ≥200 mg/dL during the OGTT.

Measurements of insulin resistance

Insulin resistance was defined by the homeostasis model assessment of insulin

resistance (HOMA) and insulin sensitivity by the quantitative insulin sensitivity check index (QUICKI). These indexes were calculated by the following formulas: HOMA-IR index = (fasting plasma insulin × fasting plasma glucose)/22.5 [24] and QUICKI = 1/[log (fasting insulin in mU/l) + log (fasting plasma glucose in mg/dL)] [25]. Glucose was expressed in mmol/L and insulin in μUI/mL. IR was defined when the value of HOMA > 4 [9].

Statistical analysis

Quantitative variables were described as mean and standard deviation (SD) or median and interquartile range (IQR) and were compared using Student-t and ANOVA or Mann–Whitney and Kruskal-Wallis tests, as appropriate.

Categorical variables were described as counts and proportions, and compared using the chi-square or Fisher's exact test. The kappa coefficient was used to analyze statistical agreement between the three differences diagnostic methods used for defining preDM and DM. Statistical analysis was performed using SPSS version 24.0 software (SPSS Inc., Chicago, Illinois, USA). All probabilities were two tailed and p values of <0.05 were regarded as significant.

RESULTS

Baseline characteristics

A total of 220 HIV-infected patients under ART were evaluated. The mean age of patients included was 45.8±11.5 years, and 60.5% of them were males. All the demographic and clinical characteristics accessed in this study are presented in Table 1, according to the presence or absence of clinical lipodystrophy (CL).

Patients with CL were older, had longer duration of the HIV infection and of ART use. Regarding anthropometric measures, patients with CL had lower weight, BMI and waist circumference mean values. Hypertension was more frequent in patients with CL, as was current and former smokers, and triglycerides median values were significantly higher than those of patients without CL. In regards to pharmaceutical therapy, the use of statins and fibrates was more frequent in patients with CL.

No differences in gender, CD4+ cell count, percentage of viral suppression, prevalence of co-infection with Hepatitis C, type of risk factor for the HIV transmission, CDC clinical categories, type of ART used and lipid profile were found between patients with or without CL.

Hemoglobin A1c

There were no patients with the diagnosis of DM using this method (HbA1c≥6.5%). Therefore we present in Table 2 the results regarding two groups: no DM (HbA1c≤5.7%) and preDM (5.7<HbA1c<6.5).

In our population 31 patients (14.1%) had the diagnosis of preDM. These patients were older and had a higher BMI, compared to the no DM patients, but had lower median level of triglycerides and less frequently used fibrate. The values obtained for HOMA-IR were higher among patients with preDM and the difference between the groups was statistically significant.

There were no differences between the diagnostic groups regarding sex, duration of HIV infection or ART use, presence or absence of CL, body composition types, WC, CD4 cell count, percentage of viral suppression,

prevalence of hepatitis C coinfection, CDC clinical category, type of ART used, lipid profile and frequency of use of statins.

Oral Glucose Tolerance Test

Considering the OGTT, 53 patients (24,1%) were classified as preDM (140mg/dL<glucose at 120 minutes<200mg/dL) and 13 patients (5,9%) with DM (glucose at 120 minutes≥200mg/dL). In Table 3, results regarding the three categories of glucose homeostasis are presented.

Patients with the diagnosis of DM were older than those with preDM, and these, in turn, were older than those without DM. A progressive stage of glucose metabolism disorder appears related to the use of IP medication, and the opposite is observed with the use of NNRTI.

The HOMA-IR index was highest among the preDM group and lowest among the no DM group.

There were no differences between the diagnostic groups regarding sex, duration of HIV infection or ART use, presence or absence of CL, body composition types, BMI, WC, CD4 cell count, percentage of viral suppression, prevalence of hepatitis C coinfection, CDC clinical category, lipid profile and frequency of use of statins or fibrates.

Fasting glucose

Forty-four patients (20%) had the diagnosis of preDM (100mg/dL<fasting glucose<126mg/dL) and 7 patients (3.2%) had the diagnosis of DM (fasting glucose≥126mg/dL). In Table 4, we present our results regarding the three categories of glucose homeostasis.

We observed that there was a significant difference regarding sex between the diagnostic groups, as all the patients with the DM diagnosis were men. In the preDM group, 47.7% of the patients were woman. The differences in age were also statistically significant, with the oldest patients being in the preDM group, and the youngest patients being in the no DM group. Regarding the different categories of body composition, we could observe that patients without DM diagnosis had the highest proportions of patients in the categories "No lipodystrophy" and "Lipoatrophy", the preDM group that the highest percentage of patients in the "Isolated central fat accumulation" category and the DM group had the highest percentage of patients in the category "Mixed form of lipodystrophy". The WC was higher among patients with DM or preDM, compared to the no DM group. However, the median value was the same between these two groups. Patients with hepatitis C coinfection were more frequently classified as no DM group, and less frequently in the preDM group. The HOMA-IR index was highest among the DM group and lowest among the no DM group.

There were no differences between the diagnostic groups regarding duration of HIV infection or ART use, presence or absence of CL, BMI, CD4 cell count, percentage of viral suppression, CDC clinical category, type of ART used, lipid profile and frequency of use of statins or fibrates.

Agreement Analyses

Kappa coefficients were computed to estimate the agreement between the three diagnostic definitions. In Table 5 we present the results from the analyses between OGTT and HbA1c. In this pair the kappa value was 0.141 (p=0.025),

which corresponds to only a slight agreement. In Table 6 we present the results from the analyses between FG and HbA1c. In this pair the kappa value was 0.013 ($p=0.848$), thus, we can say that there was no agreement at all between these two diagnostic methods. In Table 7, we present the results from the analyses between OGTT and FG. In this pair the kappa value was 0.206 ($p<0.001$), which is considered to be a fair agreement.

DISCUSSION

To our knowledge, this is the first study, conducted in HIV-infected patients, that combines the use FG, OGTT and HbA1c, to establish the diagnosis of glucose homeostasis disturbances.

Analyzing the prevalence of DM and preDM throughout these different methods, we observe that the results varied considerably. Regarding the diagnosis of DM, there were no patients identified when HbA1c was used, 13 patients (5,9% prevalence) when OGTT was used and 7 patients (3,2% prevalence) when FG was used. PreDM had a prevalence of 14,1% (31 patients) when using HbA1c, 24,1% (53 patients) when using OGTT and 20% (44 patients) when using FG. With this data we can conclude that HbA1c was the method that diagnosed the least amount of cases and that OGTT was the one that diagnosed the most cases.

In accordance with our findings, HbA1c has been found to underestimate glycemic levels in HIV-infected patients, when compared with other type of diagnostic methods, in several studies [5, 13-16, 26, 27]. Possible explanations for the lower than expected HbA1c values in these patients have been hypothesized. Low hemoglobin values [26], and situations that shorten

erythrocyte lifespan, such as hemolysis or some hemoglobinopathies, have been associated with lower HbA1c values [14]. Diop et al., have found that the discordance HbA1c-FG was positively correlated with the mean cell volume (MCV) and that hemolysis, diagnosed by a very low haptoglobin level, had a higher prevalence in the HIV-infected patients [14]. In fact, this relationship between MCV and HbA1c-FG discordance has been observed by several authors [12-16], and Glesby et al., validated it as they observed that higher values MCV emerged as the single most important factor associated with a lower HbA1c than predicted by FG. High MCV, as a marker of a greater proportion of younger erythrocytes, that had a shorter time to become glycated, suggest a greater red blood cell turnover in the HIV-infected patients [13]. The eventual relationship with drugs used in the treatment of HIV infection with these hematologic findings is difficult to study, since ART is generally used in combination.

OGTT was the method that diagnosed the highest percentage of patients with DM and preDM. Similar results have been found in the literature [18, 19, 28]. Gianotti et al., demonstrated in their study that OGTT revealed that 11% of their cohort with long-standing HIV infection had preDM or DM, undiagnosed on the basis of FG levels alone [18], while Seang et al. detected a 31% relative increase in the prevalence of DM diagnosis among HIV-infected women [19]. Epidemiological evidence has also supported this observation in the general population, especially among older patients [29]. In light of this knowledge, the 2017 EACS Guidelines recommend that HIV-infected patients with a FG diagnosis of preDM should do an OGTT in order to identify overt diabetes [11].

In regards to the characteristics that differed significantly between the diagnostic groups, we observed that there were some that were important

across all three methods, while others varied specifically depending on the method used for the assessment.

Sex was a factor that showed association with the diagnosis only when FG was used. With this method, the total number of patients that had the diagnosis of DM were male, and in the preDM group there was also a higher prevalence of male (52,3% versus 47,7% female). This characteristic has had antagonistic findings in the literature. Some authors have reported a lack of significant differences between sexes when considering the risk factors for glucose homeostasis disturbances in HIV patients [18] while others, in agreement with our findings, stated that male sex was associated with increased risk of new-onset DM [6, 30].

In all three methods, a progressive stage of glucose homeostasis disturbance was associated with older age. This finding is congruent with the great majority studies done on the subject [2-6, 8, 30, 31]. It has been highlighted in recent literature that, after the introduction of ART, which has dramatically reduced HIV-related mortality and morbidity, increasing substantially the longevity, HIV-infected individuals have a potential of developing metabolic complications, that is comparable to that of the general population [2]. In these patients, the importance of traditional cardio-metabolic risk factors should be emphasized, since these are likely to exert an equal influence on HIV-infected patients as they do in the general population [2]. On the other hand, there have been studies that suggest that the aging process might be premature or accelerated in these patients, leading to the manifestation of metabolic complications earlier in life [3]. This highlights the importance of closely monitoring for the development of cardio-metabolic abnormalities in these patients.

Regarding the duration of HIV infection and ART use, we observed that, throughout all the diagnostic methods, there wasn't a significant difference between the groups. Therefore, we can presume that, in our population, these factors had little influence in the development of glucose homeostasis disturbances. This contrasts with findings in the literature that suggest that a higher prevalence of DM is associated with a higher duration of HIV infection and ART use [2, 4, 32], but, is in agreement with a study done by Araújo et al., which have also found a lack of association between the duration of infection and the development of glucose homeostasis disturbances [33].

BMI was considered to be significantly higher in preDM patients, compared to the no DM ones, only when HbA1c was used for the assessment. This finding is corroborated by several authors [4-6, 8, 30-32] that described a significant association between a higher BMI and the presence of disturbances of glucose homeostasis in HIV-infected patients. Additionally to the BMI, abdominal fat accumulation or trunk obesity has been identified as a factor primarily associated with the prevalence of disturbances of glucose homeostasis in HIV-infected patients [9, 19, 28, 32-35], just as described in the general population. In our study, when FG was used for the assessment, there was a significant association between WC and the diagnosis. This parameter was higher in DM and preDM patients, when compared with the no DM ones. Also in this diagnostic method, we obtained significant differences regarding the classes of body composition, with most significant differences observed in the Isolated central fat accumulation (highest percentage of patients in the preDM group) and mixed forms of lipodystrophy (highest percentage of patients in the DM group), which mirror the effect of this higher WC in these diagnostic groups. It has in fact been

reported that abdominal fat accumulation is a higher contributor to the disturbances of glucose metabolism than the lipoatrophy associated with the acquired lipodystrophy of HIV infection [9]. Endocrine activity of adipose tissue takes a central place in the pathogenesis of metabolic disorders [36], thus it makes sense, pathogenically, that this relationship occurs. There were no differences in the diagnostic groups regarding the presence of absence of CL in neither of the diagnostic methods.

Hepatitis C coinfection has been found to be associated with the development of glucose homeostasis disturbances among HIV-infected patients [8, 31, 33]. In our study, when FG was used for assessment, Hepatitis C coinfection had a prevalence of 33,5% (56 patients) in the no DM group, 28,6% (2 patients) in the DM group and 14,3% (6 patients) in the preDM group. The no DM group had the highest percentage of patients with coinfection, hence, we could hypothesize that coinfection was not related to the development of glucose homeostasis disturbances. However, we have to keep in mind that in the preDM and DM group the number of patients is very reduced. Hence, the small sample size may be a limitation for the interpretation of this finding.

The association between ART and the development of diabetes has been frequently described throughout the literature [2, 5, 6, 28]. When we analyzed the type of ART used, only when the OGTT method was applied, there were significant differences. In this group, we observed that progressive stage of glucose homeostasis disturbance was positively associated with the use of PIs and negatively associated with the use of NNRTIs. It has in fact been reported that PI-based regimens might be associated with the development and acceleration of the progression of metabolic complications [2, 32], although this

association is not consensual among the literature [6, 8, 33, 35, 37, 38]. Slama et al. have reported that certain ART (PIs, NNRTIs and zidovudine) were associated with the HbA1c-FG discordance [16] but, regarding specifically the use of HbA1c for the assessment, Kim et al., similarly to our findings, have reported a lack of association between all types of ART and the diagnosis of diabetes [39]. In other studies, NNRTIs were recognized as an alternative regimen to PIs in patients with metabolic complication, because these had a lower prevalence of such complications [2, 38]. On the other hand, NRTIs have been associated with an increased risk of glucose metabolism disturbances [6, 30, 33, 37, 38], and with the HbA1-FG discordance in the assessment of HIV-infected patients, suggesting that, in this patients, HbA1c shouldn't be used for the assessment of glycemia [15]. In our study, there were no significant association between the use of NRTIs and the development of glucose homeostasis disturbances. It is, however, extremely difficult to determine which drug is responsible for the risk of glucose metabolism disturbances, since they are always used in combination and, also, therapeutic changes often occur during the course of the disease.

Despite the euglycemic insulin clamp technique being the gold standard technique for the study of tissue sensitivity to insulin [40], we used easier to perform methods, HOMA-IR and QUICKI indexes, that have shown a strong correlation with the gold standard, and good correlation between each other, allowing us to have a robust estimate of insulin sensitivity [18, 24, 25]. The HOMA-IR index was higher in the preDM group comparing to the no DM group when we used the HbA1c, lowest in the no DM group and highest in the DM group when we used the FG, and highest in the preDM group and lowest in the no DM group when we used the OGTT. The QUICKI index had exactly the

opposite results. These results support the evidence that progressive stages of glucose metabolism disorders are associated with progressive stages of insulin resistance. In the case of OGTT, where the preDM group had indexes more altered than the DM group, a possible explanation may be that, in a DM state, the insulin deficiency is superior to that of the preDM state. Hence, in both preDM and DM we have insulin resistance but, since the insulin deficiency is greater in the DM state, the calculation of these indexes is affected, becoming less pronounced.

With the exception of HbA1c, which detected a significant difference between the diagnostic groups regarding the triglycerides, there were no other abnormalities in the lipid profile that were significantly different between the groups using the other methods. De Wit et al, reported triglycerides, HDL cholesterol and total cholesterol to be associated with new-onset diabetes [6]. However, the absence of differences in the lipid profile was also found in other studies [18]. In the HbA1c method the levels of triglycerides in preDM patients were lower than the ones observed in no DM patients. The use of fibrates was also lower in the preDM group comparing with the no DM one. This finding makes sense, since this is the main medication used to treat hypertriglyceridemia. Since there were no significant differences regarding CL, body composition types and WC, and the difference observed in BMI indicated an overweight in preDM patients, we could not justify this finding from the data that we have available.

Divergently from what has been described in the literature, there was no association between the glucose homeostasis disturbances and use of statins [8]. Lichtenstein et al., have described a 14% increase in the rate of incident of diabetes per year of statin use, which was on par with the estimates from the

general population [8]. Since this was not a characteristic that significantly differed between our diagnostic groups, we can infer that the use of these drugs was not long enough to cause the development of such complications or that they didn't have a significant impact on the metabolic status of our patients.

There were no differences in HIV-related parameters between the different groups of glucose homeostasis disturbances. Research has associated a lower CD4 cell count with higher prevalence of glucose homeostasis disturbances [4, 18], and a count of <500 cells/mm^3 was found to be strongly associated with HbA1c-FG discordance [16]. Although we had diagnostic groups throughout our study that had counting bellow this level, the difference between them was never significant. Thus, we can hypothesize that this characteristic had a small impact in the development of this kind of complications.

In our agreement analyses we used the kappa coefficient, which is a robust statistic, useful for either interrater or intrarater reliability testing. It can range from −1 to +1, where 0 represents the amount of agreement that can be expected from random chance, and 1 represents perfect agreement between the raters. Kappa values are considered to represent a slight agreement when they are between 0-0.20 and fair agreement when they are between 0.21-0.40 [41]. Hence, in face of our results, we can conclude that the agreement between FG-OGTT was fair (0.206) and between FG-HbA1c (0.013) and OGTT- HbA1c (0.141) was slight. Consequently, we can say that these diagnostic methods agree much less than would be expect only by chance.

Limitations

This study had some limitations, mainly related to the observational design and the cross-sectional nature of our analyses that prevent us from taking any conclusions regarding causality. Although we included all patients referred to our department, we cannot exclude bias in the referral, since some patients could have been referred because they already had some suspicion of DM or other metabolic disorder. Therefore, we might have selected a study population rich in metabolic and endocrine complications. Consequently, these results cannot be extrapolated for the total HIV population.

CONCLUSIONS

In our study it was clear that disturbances of glucose homeostasis was a prevalent problem, specifically preDM, which had values of 14,1%, 24,1% and 20% prevalence, depending on the method used for the diagnosis. Hence, more sensitive diagnostic tools are essential for prevention of DM complications in this population. Our results indicate that HbA1c underestimated glycaemia levels, and that OGTT might in fact allow an earlier diagnosis of glucose homeostasis disturbances, since it was the method that had a higher capacity to detect them. Therefore, in the HIV population, it would be prudent for the medical practitioner's to use direct measures of glycaemia (FG or OGTT) to diagnose glucose homeostasis disturbances, or, perhaps, consider establishing lower HbA1c thresholds to determine this diagnosis.

List of abbreviations:

HIV – human immunodeficiency virus, AIDS – acquired immune deficiency syndrome, ART – antiretroviral therapy, DM – diabetes mellitus, EACS – European AIDS Clinical Society, FG – fasting glucose, OGTT – oral glucose tolerance test, HbA1c - hemoglobin A1c / glycated Hemoglobin, preDM – prediabetes, ADA – American Diabetes Association, cART – combined antiretroviral therapy, BMI – body mass index, WC – waist circumference, TC – total cholesterol, LDL – low density lipoprotein, HDL – high density lipoprotein, HOMA - homeostatic model assessment, QUICKI - quantitative insulin sensitivity check index, CL – clinical lipodystrophy, MCV – mean cell volume, CDC – centers for disease control and prevention, PI – protease inhibitor, NNRTI – non-nucleoside reverse transcriptase inhibitor, NRTI – nucleoside reverse transcriptase inhibitor.

Competing interests

The authors declare that they have no competing interests

Authors' contributions

ARC conceived the study, participated in its design, in the acquisition of data and drafted the manuscript; FAM participated in the acquisition of data; ACS performed the statistical analysis; ASP participated in the acquisition of data and revised the manuscript; AS revised critically the manuscript; DC revised critically the manuscript; PF participated in the acquisition of data, in the design of the study and revised critically the manuscript. All authors read and approved the final manuscript.

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Table 1. Sample's baseline characteristics, according to the presence of CL.

	With CL	Without CL	P value
n (%)	115 (52.3)	105 (47.7)	
Sex [n(%)]			0.099
Male	76 (66.1)	57 (54.3)	
Female	39 (33.9)	48 (45.7)	
Age [years, mean (SD)]	47.5 (11.29)	43.82 (11.49)	0.017
Duration of HIV infection [years, median (IR)]	9.00 (5.0)	6.00 (6.0)	0.001
cART [years, median (IR)]	8.00 (5.0)	5.00 (5.5)	<0.001
Weight [Kg, mean (SD)]	64.14 (12.81)	73.87 (12.61)	<0.001
Height [m, mean (SD)]	1.65 (0.09)	1.65 (0.09)	0.765
BMI [(kg/m2), mean (SD)]	23.56 (3.84)	27.15 (4.50)	<0.001
Waist circumference [cm, mean (SD)]	88.40 (10.80)	95.08 (12.05)	<0.001
CD4 cell count [cells/mm3, median (IR)]	554.00 (385)	479.00 (300)	0.238
HIV RNA (< 50) [n (%)]	100 (100)	92 (100)	
Hepatitis C co-infection [n (%)]	34 (29.8)	30 (29.4)	0.999
Hypertension [n(%)]	45 (39.1)	23 (21.9)	0.009
HIV risk factor [n (%)]			0.162
Intravenous drug user	1 (25)	3 (15.8)	
Homosexual contact	0 (0)	2 (10.5)	
Heterosexual contact	2 (50)	14 (73.7)	
Others	1 (25)	0 (0)	
CDC clinical categories [n (%)]			0.389
A	63 (54.8)	56 (53.3)	
B	1 (0.9)	4 (3.8)	
C	51 (44.3)	45 (42.9)	
ART [n (%)]			
IP	61 (53.0)	62 (59.0)	0.447
NNRTI	55 (47.8)	47 (44.8)	0.749
NRTI	113 (98.3)	97 (92.4)	0.051
Smoking history [n (%)]			0.032
Never	38 (33.3)	53 (50.5)	
Current	56 (49.1)	36 (34.3)	
Former	20 (17.5)	16 (15.2)	
Total cholesterol [mg/dL, mean (SD)]	221.89 (53.21)	227.78 (57.76)	0.433
LDL- cholesterol [mg/dL, mean (SD)]	129.39 (48.08)	139.95 (45.46)	0.097
HDL- cholesterol [mg/dL, mean (SD)]	46.52 (14.77)	49.47 (13.26)	0.123
Triglycerides [mg/dL, median (IR)]	215.50 (214.5)	171 (154)	0.007
Statin use [n (%)]	33 (28.7)	13 (12.4)	0.005
Fibrate use [n (%)]	41 (35.7)	24 (22.9)	0.054

CL: clinical lipodystrophy; cART: combination antiretroviral therapy; BMI: body mass index; ART: antiretroviral therapy; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; HOMA: homeostatic model assessment; QUICKI: quantitative insulin sensitivity check index.; SD: standard deviation; IR: interquartile range.

Table 2. Sample's characteristics, according to the presence of preDM or no DM, accessed by HbA1c.

	HbA1c		P value
	<5.7%	**5.7-6.4%**	
n (%)	189 (85.9)	31 (14.1)	
Sex [n(%)]			0.623
Male	116 (61.4)	17 (54.8)	
Female	73 (38.6)	14 (45.2)	
Age [years, mean (SD)]	44.99 (11.30)	50.35 (11.89)	0.016
Duration of HIV infection [years, median (IR)]	8.00 (6.0)	8.00 (7.0)	0.698
cART [years, median (IR)]	6.00 (6.5)	7.00 (7.0)	0.136
Clinical lipodystrophy [n(%)]			0.909
Without CL	91 (48.1)	14 (45.2)	
With CL	98 (51.9)	17 (54.8)	
Body Composition [n(%)]			0.469
No lipodystrophy	28 (15.3)	3 (10)	
Isolated central fat accumulation	59 (32.2)	10 (33.3)	
Lipoatrophy	52 (28.4)	6 (20.0)	
Mixed form of lipodystrophy	44 (24.0)	11 (36.7)	
BMI [(kg/m2), mean (SD)]	25.01 (4.49)	26.90 (4.46)	0.031
Waist circumference [cm, mean (SD)]	90.93 (11.55)	95.23 (13.18)	0.065
CD4 cell count [cells/mm3, median (IR)]	500.00 (345)	528.00 (312)	0.819
HIV RNA (< 50) [n (%)]	165 (100)	27 (100)	
Hepatitis C co-infection [n (%)]	57 (30.8)	7 (22.6)	0.474
CDC clinical categories [n (%)]			0.093
A	107 (56.6)	12 (38.7)	
B	5 (2.6)	0 (0)	
C	77 (40.7)	19 (61.3)	
ART [n (%)]			
IP	106 (56.1)	17 (54.8)	0.999
NNRTI	88 (46.6)	14 (45.2)	0.999
NRTI	182 (96.3)	28 (90.3)	0.152
HOMA-IR index [median (IR)]	1.62 (1.46)	2.51 (5.13)	0.023
QUICKI index [median (IR)]	0.36 (0.05)	0.33 (0.08)	0.023
Total cholesterol [mg/dL, mean (SD)]	225.62 (55.42)	219.00 (55.82)	0.544
LDL- cholesterol [mg/dL, mean (SD)]	133.54 (47.45)	140.20 (44.62)	0.473
HDL- cholesterol [mg/dL, mean (SD)]	48.27 (14.44)	45.80 (11.83)	0.374
Triglycerides [mg/dL, median (IR)]	203.00 (198.0)	139.00 (133.8)	0.010
Statin use [n (%)]	41 (21.7)	5 (16.1)	0.640
Fibrate use [n (%)]	61 (32.3)	4 (12.9)	0.048

preDM: prediabetes; DM: diabetes mellitus; HbA1c: glycated haemoglobin; CL: clinical lipodystrophy; cART: combination antiretroviral therapy; BMI: body mass index; ART: antiretroviral therapy; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; HOMA: homeostatic model assessment index; QUICKI: quantitative insulin sensitivity check index; SD: standard deviation; IR: interquartile range.

Table 3. Sample's characteristics according to the presence of DM, preDM and no DM, accessed by OGTT.

	Glucose at 120 minutes			P value
	<140 mg/dL	**140-200 mg/dL**	**≥200 mg/dL**	
n (%)	154 (70)	53 (24.1)	13 (5.9)	
Sex [n(%)]				0.061
Male	101 (65.6)	26 (49.1)	6 (46.2)	
Female	53 (34.4)	27 (50.9)	7 (53.8)	
Age [years, mean (SD)]	43.38 (10.24)	50.36 (12.13)	55.00 (13.55)	<0.001
Duration of HIV infection [years, median (IR)]	8.00 (6.0)	7.00 (6.0)	10.00 (8.0)	0.980
cART [years, [median (IR)]	6.00 (5.3)	6.00 (7.0)	9.00 (9.0)	0.566
Clinical lipodystrophy [n(%)]				0.148
Without CL	78 (50.6)	24 (45.3)	3 (23.1)	
With CL	76 (49.4)	29 (54.7)	10 (76.9)	
Body Composition [n(%)]				0.078
No lipodystrophy	23 (15.5)	7 (13.5)	1 (7.7)	
Isolated central fat accumulation	50 (33.8)	17 (32.7)	2 (15.4)	
Lipoatrophy	45 (30.4)	11 (21.2)	2 (15.4)	
Mixed form of lipodystrophy	30 (20.3)	17 (32.7)	8 (61.5)	
BMI [(kg/m2), [median (IR)]	24.53 (5.83)	25.35 (6.39)	25.51 (3.26)	
Waist circumference [cm, median (IR)]	90.5 (16.0)	91.0 (17.8)	95.0 (8.5)	0.687
CD4 cell count [cells/mm3, [median (IR)]	512.5 (336.0)	500.0 (311.0)	456.0 (509)	0.569
HIV RNA (< 50) [n (%)]	138 (100)	44 (100)	10 (100)	
Hepatitis C co-infection [n (%)]	47 (30.9)	15 (28.8)	2 (16.7)	0.655
CDC clinical categories [n (%)]				0.252
A	90 (58.4)	24 (45.3)	5 (38.5)	
B	4 (2.6)	1 (1.9)	0 (0)	
C	60 (39.0)	28 (52.8)	8 (61.5)	
ART [n (%)]				
IP	77 (50)	36 (67.9)	10 (76.9)	0.023
NNRTI	82 (53.2)	17 (32.1)	3 (23.1)	0.005
NRTI	148 (96.1)	51 (96.2)	11 (84.6)	0.188
HOMA-IR index [median (IR)]	1.41 (1.54)	2.37 (2.48)	1.94 (3.17)	<0.001
QUICKI index [median (IR)]	0.36 (0.06)	0.34 (0.05)	0.35 (0.06)	<0.001
Total cholesterol [mg/dL, median (IR)]	224.00 (67)	224.00 (79)	234 (86)	0.743
LDL- cholesterol [mg/dL, median (IR)]	130.00 (70)	135 (66)	156 (79)	0.843
HDL- cholesterol [mg/dL, median (IR)]	49 (19)	44 (20)	52 (15)	0.314
Triglycerides [mg/dL, median (IR)]	186.00 (176.5)	223.000 (258.5)	170.000 (101.0)	0.131
Statin use [n (%)]	31 (20.1)	9 (17.0)	6 (46.2)	0.072
Fibrate use [n (%)]	43 (27.9)	21 (39.6)	1 (7.7)	0.061

preDM: prediabetes; DM; diabetes mellitus; OGTT: oral glucose tolerance test; CL: clinical lipodystrophy; cART: combination antiretroviral therapy; BMI: body mass index; ART: antiretroviral therapy; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; HOMA: homeostatic model assessment index; QUICKI: quantitative insulin sensitivity check index; SD: standard deviation; IR: interquartile range.

Table 4. Sample's characteristics according to the presence of DM, preDM and no DM, accessed by FG.

	Fasting glucose			P value
	<100 mg/dL	**100-126 mg/dL**	**≥126 mg /dL**	
n (%)	169 (76.8)	44 (20)	7 (3.2)	
Sex [n(%)]				0.049
Male	103 (60.9)	23 (52.3)	7 (100)	
Female	66 (39.1)	21 (47.7)	0 (0)	
Age [years, [median (IR)]	43.00 (15)	51.50 (15)	45.00 (14)	0.027
Duration of HIV infection [years, [median (IR)]	8.00 (6.0)	8.00 (5.8)	8.00 (6.0)	0.782
cART [years, [median (IR)]	6.00 (7.0)	6.00 (5.8)	8.00 (6.0)	0.408
Clinical lipodystrophy [n(%)]				0.082
Without CL	76 (45.0)	27 (61.4)	2 (28.6)	
With CL	93 (55)	17 (38.6)	5 (71.4)	
Body Composition [n(%)]				0.004
No lipodystrophy	26 (15.8)	4 (9.8)	1 (14.3)	
Isolated central fat accumulation	46 (27.9)	22 (53.7)	1 (14.3)	
Lipoatrophy	52 (31.5)	6 (14.6)	0 (0)	
Mixed form of lipodystrophy	41 (24.8)	9 (22.0)	5 (71.4)	
BMI [(kg/m2), [median (IR)]	24.37 (5.84)	26.07 (5.45)	26.03 (3.36)	0.052
Waist circumference [cm, [median (IR)]	88.00 (16.5)	95.00 (13.5)	95.00 (15.0)	0.005
CD4 cell count [cells/mm3, [median (IR)]	486.00 (344)	525.00 (298)	605.00 (382)	0.643
HIV RNA (< 50) [n (%)]	151 (100)	35 (100)	6 (100)	
Hepatitis C co-infection [n (%)]	56 (33.5)	6 (14.3)	2 (28.6)	0.034
CDC clinical categories [n (%)]				0.398
A	89 (52.7)	27 (61.4)	3 (42.9)	
B	3 (1.8)	2 (4.5)	0 (0)	
C	77 (45.6)	15 (34.1)	4 (57.1)	
ART [n (%)]				
IP	96 (56.8)	23 (52.3)	4 (57.1)	0.885
NNRTI	79 (46.7)	20 (45.5)	3 (42.9)	0.999
NRTI	163 (96.4)	41 (93.2)	6 (85.7)	0.157
HOMA-IR index [median (IR)]	1.45 (1.31)	3.18 (2.57)	9.27 (6,79)	<0.001
QUICKI index [median (IR)]	0.36 (0.05)	0.32 (0.04)	0.28 (0.04)	<0.001
Total cholesterol [mg/dL, median (IR)]	220.00 (66)	240.50 (86)	234.00 (79)	0.061
LDL- cholesterol [mg/dL, median (IR)]	127.00 (67)	149.00 (62)	146.00 (74)	0.136
HDL- cholesterol [mg/dL, median (IR)]	47.00 (18)	49.00 (22)	41.00 (22)	0.651
Triglycerides [mg/dL, median (IR)]	189.50 (197.8)	214.50 (207.8)	184.00 (88.0)	0.975
Statin use [n (%)]	35 (20.7)	8 (18.2)	3 (42.9)	0.312
Fibrate use [n (%)]	50 (29.6)	15 (34.1)	0 (0)	0.200

preDM: prediabetes; DM; diabetes mellitus; FG: fasting glucose; CL: clinical lipodystrophy; cART: combination antiretroviral therapy; BMI: body mass index; ART: antiretroviral therapy; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; HOMA: homeostatic model assessment index; QUICKI: quantitative insulin sensitivity check index.; SD: standard deviation; IR: interquartile range.

Table 5. Analysis of the agreement between HbA1c and Glucose at 120 minutes during an OGTT.

		Glucose at 120 minutes		Total
		<140 mg/dL	**140-200 mg/dL**	
HbA1c	<5.7%	140	42	182
	5.7-6.4%	14	11	25
Total		154	53	207
Kappa Coefficient = 0.141 (p = 0.025)				

HbA1c: glycated haemoglobin; OGTT: oral glucose tolerance test.

Table 6. Analysis of the agreement between HbA1c and FG.

		Fasting glucose		Total
		<100 mg/dL	**100-126 mg/dL**	
HbA1c	<5.7%	148	39	187
	5.7-6.4%	21	5	26
Total		169	44	213
Kappa Coefficient = 0.013 (p = 0.848)				

HbA1c: glycated haemoglobin; FG: fasting glucose.

Table 7. Analysis of the agreement between FG and Glucose at 120 minutes during a OGTT.

		Glucose at 120 minutes			Total
		<140 mg/dL	**140-200 mg/dL**	**≥200 mg/dL**	
Fasting glucose	<100 mg/dL	128	34	7	169
	100-126 mg/dL	24	17	3	44
	≥126 mg /dL	2	2	3	7
Total		154	53	13	220
Kappa Coefficient = 0.206 (p < 0.001)					

FG: fasting glucose; OGTT: oral glucose tolerance test.

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ANEXOS

Normas da revisa BioMed Central Infectious Diseases

Parecer da Comissão de Ética para a Saúde e Autorização do Concelho de Administração do Centro Hospitalar São João

Research article

Criteria

Research articles should report on original primary research, but may report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research will not be considered.

Preparing your manuscript

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
    - or for non-clinical or non-research studies a description of what the article reports
- list the full names, institutional addresses and email addresses for all authors

- if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below

- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively (before enrollment of the

first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval.

If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
    - All data generated or analysed during this study are included in this published article [and its supplementary information files].

- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
- Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

BioMed Central also requires that authors cite any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier (such as a DOI) and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs. For example:

Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014.http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]

Competing interests

All financial and non-financial competing interests must be declared in this section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section.

Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

If you do not have anyone to acknowledge, please write "Not applicable" in this section.

Group authorship (for manuscripts involving a collaboration group): if you would like the names of the individual members of a collaboration Group to be searchable through their individual PubMed records, please ensure that the title of the collaboration Group is included on the title page and in the submission system and also include collaborating author names as the last paragraph of the “Acknowledgements” section. Please add authors in the format First Name, Middle initial(s) (optional), Last Name. You can add institution or country information for each author if you wish, but this should be consistent across all authors.

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This section is optional. You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. The reference numbers must be finalized and the reference list fully formatted before submission.

Examples of the BioMed Central reference style are shown below. Please ensure that the reference style is followed precisely.

Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link (e.g. for blogs) they should be included in the reference.

Example reference style:

Article within a journal

Smith JJ. The world of science. Am J Sci. 1999;36:234-5.

Article within a journal (no page numbers)

Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. BMC Med. 2013;11:63.

Article within a journal by DOI

Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement

Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Book chapter, or an article within a book

Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306. OnlineFirst chapter in a series (without a volume designation but with a DOI) Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Complete book, authored

Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

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University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

Organization site

ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.

Tables and captions

When preparing tables, please follow the formatting instructions below.

- Tables should be numbered and cited in the text in sequence using Arabic numerals (i.e. Table 1, Table 2 etc.).
- Tables less than one A4 or Letter page in length can be placed in the appropriate location within the manuscript.
- Tables larger than one A4 or Letter page in length can be placed at the end of the document text file. Please cite and indicate where the table should appear at the relevant location in the text file so that the table can be added in the correct place during production.
- Larger datasets, or tables too wide for A4 or Letter landscape page can be uploaded as additional files. Please see [below] for more information.
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- Table titles (max 15 words) should be included above the table, and legends (max 300 words) should be included underneath the table.
- Tables should not be embedded as figures or spreadsheet files, but should be formatted using 'Table object' function in your word processing program.
- Color and shading may not be used. Parts of the table can be highlighted using superscript, numbering, lettering, symbols or bold text, the meaning of which should be explained in a table legend.
- Commas should not be used to indicate numerical values.

Comissão de Ética para a Saúde do HSJ

Parecer

Projecto de investigação: "Screening type 2 Diabetes mellitus in HIV-infected patients – fasting glucose, A1C or oral glucose tolerance test – which method to choose?".

Promotores:
- Não aplicável.

- Pertinência do estudo

- Trata-se de um estudo de coorte, retrospectivo, a realizar no âmbito da tese de Mestrado Integrado em Medicina na Faculdade de Medicina da Universidade do Porto (FMUP), que tem como objectivo principal, comparar métodos de diagnóstico de diabetes mellitus – glicose em jejum, hemoglobina A1C e prova de tolerância oral à glicose – em doentes com infecção VIH sob terapêutica antiretrovírica seguidos em consulta de Endocrinologia.
  - Serão incluídos todos os indivíduos com infecção VIH seguidos na consulta de Endocrinologia do Centro Hospitalar de S. João, entre janeiro de 2004 e março de 2016.
  - O estudo terminará em março de 2017 e não terá nem precisará de qualquer apoio financeiro.
  - Todos os dados a colher de forma a anónima (sócio-demográficos, antropométricos, clínicos, virológicos, analíticos e terapêuticos) são pertinentes e adequados aos objectivos do estudo.
    - O estudo é pertinente, importante e está bem fundamentado.
    - O protocolo de estudo, os critérios de inclusão e de exclusão estão suficientemente detalhados e não levantam quaisquer questões do foro ético.
    - A Investigadora Principal, Ana Rita Moreira Coelho, estudante do 6º ano do curso de Medicina da FMUP, tendo como elo de ligação (e orientadora da Tese) a Médica especialista de Endocrinologia, a Professora Paula Freitas (especialista do Serviço de Endocrinologia do Hospital de S. João EPE), dispõe das competências técnica e científica para a realização do estudo.
    - O estudo será realizado no Serviço de Endocrinologia do Hospital de S. João, EPE e dispõe da autorização para a sua realização pelo seu Director, Professor Davide Carvalho. O serviço proponente dispõe das condições necessárias para a realização do estudo.

– Beneficio/Risco

- Dada a natureza retrospectiva do estudo, não haverá riscos, incómodos ou benefícios para os participantes.

– Respeito pela liberdade e autonomia do sujeito do ensaio

- Dada a natureza retrospectiva do estudo, não há necessidade de proceder à obtenção do consentimento informado.

– Confidencialidade dos dados

- A confidencialidade e a privacidade dos dados são garantidas.

– Indemnização por danos

Não aplicável.

– Continuação do tratamento

Não aplicável.

- Propriedade dos dados

Não aplicável.

Conclusão

Em face da análise do protocolo de "Screening type 2 Diabetes mellitus in HIV-infected patients – fasting glucose, A1C or oral glucose tolerance test – which method to choose?", proponho a sua aprovação pela CES do HSJ/FMUP.

Porto, 22 de julho de 2016

O Relator
Prof. Manuel Vaz Silva

197-16

Unidade de Investigação

Tomei conhecimento. Nada a opor.

12 de Setembro de 2016

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

AUTORIZADO

CONSELHO DE ADMINISTRAÇÃO REUNIÃO DE 22 SET 2016

Presidente do Conselho de Administração

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DIRECÇÃO CLINICA
16/9/2016

Aprovado. Ao CA.

(Prof.ª Doutora Ana Azevedo)

Exmo. Senhor
Presidente do Conselho de Administração do
Centro Hospitalar de S. João – EPE

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Ana Rita Moreira Coelho

Título do projecto de investigação: Screening type 2 diabetes mellitus in HIV-infected patients – fasting glucose, A1C or oral glucose tolerance test – which method to choose?

Pretendendo realizar no Serviço de Endocrinologia do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 05 de Julho de 2016

O INVESTIGADOR/PROMOTOR

Ana Rita Coelho

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)

NÃO ☐

NÃO APLICÁVEL ☒

8. TERMO DE RESPONSABILIDADE

Eu, Ana Rita Moreira Coelho , abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 5 de Julho de 2016

Ana Rita Coelho

O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO/FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

emitido na reunião plenária da CES de 22 / Julho / 2016

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.